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10/719,990	11/21/2003	Alan Howe	421/73/2	1736

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14,36,38,39 and 41-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14, 36, 38-39 and 41-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 8/06/2008 in response to the previous Non-Final Office Action (2/06/2008) is acknowledged and has been entered.

Claims 1-4, 6-14, 36, 38-39 and 41-47 are currently pending and under consideration.

Rejections Maintained:.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6-9, 36, 38-39 and 41-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over McHahan et al. (Analytical Biochemistry 1996; 236: 101-106, *of record*), or Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*) in view of Wagner et al. (US 7,183,392, 2007), Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116).

McMahan et al. disclose a conjugate comprising polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical to the molecule shown in the instant specification in Figure 7 (see page 103, Figure 1). For example, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, McMahan *et al.* teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan *et*

al. teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Lastly, the reference teaches that the conjugate is a unique reagent, which can be used for the detection of histidine-tagged proteins (Title).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Although Molecular Probes does not specifically teach that the detectable moiety is conjugated to the polydentate chelator at a site other than a potential metal ion coordination site, the claimed limitation does not appear to result in a manipulative difference between the claimed product and that disclosed by the prior art because the specification teaches that biotin-conjugated NTA is commercially available through Molecular probes or can be synthesized following the method of McMahan (described above). Thus, the conjugate appears to be the same as the prior art. Similarly, while Molecular Probes does not specifically teach that the conjugate is soluble in an aqueous medium, the claimed functional limitation would be an inherent property of the referenced product because as evidenced by McMahan *et al.* (*supra*), biotin and nitriloacetic acid conjugates are soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Thus, the claimed "conjugate" appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

As such, both McMahan et al. and Molecular Probes teach a heterobifunctional conjugate comprising a polydentate chelator, a linker and a detectable moiety. However, Neither McMahan et al. nor Molecular Probes explicitly teach that the metal ion is Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} or that the binding solution is in a pH range of 5 to 7.0.

Wagner et al. teach that nitrilotriacetic acid, (NTA), coordinated with metals such as Ni, Co, Fe and Cu bind His-tags of 6 to 9 amino acids column 19, Lines 15-19).

Chaga et al. reviews twenty-five years of immobilized metal ion affinity chromatography (Title). In particular, Chaga et al. teaches that immobilized metal ion affinity chromatography, referred to herein as IMAC, is a separation principle that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein the metal ions can be divided into three categories (hard, intermediate, and soft) based on their preferential activity towards nucleophiles, wherein hard metals such as Fe3+, Ca2+, Al3+ show preference for oxygen, soft metals such as Cu+, Hg2+, ect. prefer sulfur, and intermediate metals such as Cu2+, Ni2+, Zn2+, Co2+ coordinate to nitrogen, oxygen and sulfur (page 314, 2.Metal ion affinity). For example, the reference teaches that IMAC has seen extensive work in the purification of proteins from complex biological samples such as the use of Cu2+, Ni2+ and Zn2+ for the purification of proteins having exposed Histidine residues, as well as, the use of Fe3+ and Ga3+ for the enrichment of phosphorylated proteins and peptides (page 315, Historical development of IMAC, in particular, last paragraph of page 315, 1st paragraph of 316 and 3rd full paragraph of page 317). The reference further teaches that there are only a few commercially available adsorbents such as IDA and NTA which offer a maximum of tri-(IDA) or tetra (NTA) complexes with the metal ion (page 318, Versatility of the chelating ligands). Lastly, the reference teaches that different absorption selectivity's for a protein within the same sample can be achieved based on whether one uses a hard or intermediate immobilized metal ion. For example, the reference teaches that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu2+ at neutral pH (page 320, Metal ion type).

Zachariou et al. teach the binding properties of immobilised O-phosphoserine (im-OPS) and 8-hydroxyquinoline (im-8-HQ) with immobilised iminodiacetic acid, also referred to as IDA, as the

control system in combination with the hard Lewis metal ions, Al3+, Ca2+, Fe3+, Yb3+, and the borderline metal ion, Cu2+, over a pH range of 5.5 to 8.0 (abstract). With regards to the pH, the reference teaches that with a incubation/equilibrium buffer of 0.5 M or 0.06M ionic strength, fewer proteins bound to these hard Lewis metal ion IMAC adsorbents as the pH became increasingly alkaline, which is opposite to what is observed with protein with the borderline Lewis metal ion IMAC systems (page 111, 1st column, last paragraph bridging 2nd column).

Thus, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference to as to modify the heterobifunctional conjugate as taught by McMahan et al. or Molecular probes with Fe3+ in view of the teachings of Wagner et al. One would have been motivated to do so because Wagner et al. teaches that NTA coordinated with Fe3+ binds His-Tags. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the heterobifunctional conjugate as taught by McMahan et al. or Molecular probes with Fe3+ in view of the teachings of Wagner et al., one would achieve a metal chelate which recognizes a His tag.

Secondly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference so as to substitute the metal ion which coordinates to the heterobifunctional conjugate as taught by McMahan et al. or Moleucular Probes to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by Chaga et al., that different metals such as hard Lewis metals may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Similarly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to use a lower pH binding solution when detecting proteins using hard Lewis metal ions such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by both Chaga and Wagner, that hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

In response to this rejection, Applicants respectfully disagree that the Patent Office has presented a prima facie case of unpatentability of the pending claims over the cited references. For example, Applicants assert that the Patent Office has not provided motivation to modify the heterobifunctional conjugate as taught by McMahon or Molecular Probes with Fe3+ in view of the

teachings of Wagner because Wagner et al .teaches that NTA coordinated to Fe3+ binds His -Tags. In particular, Applicants assert that the Patent Office has not provided any motivation to remove the Ni2+ ion from the conjugates of McMahan and/or Molecular Probes and replace it with a different ion merely in order to use the conjugates for exactly the same function. In addition, Applicants submit that there is no advantage that can be seen in making such a modification, and thus, there is no support for the contention that one of ordinary skill in the art would have been motivated to do so. With regards to the Chaga et al. reference, Applicants assert that the Patent Office's contentions of Chaga represent overly broad readings of this reference. For example, Applicants contend that Chaga et al. suggests that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from which would be adsorbed to immobilized Cu2+ at neutral pH; not that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Fe3+ at neutral pH. As such, Applicants asset that there is no motivation in Chaga for employing a binding solution with a pH range from about 5.0 to about 7.0 as recited in the instant claims. Moreover, Applicants contend that both Wagner et al .and Zachariou fail to cure this deficiency.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner recognizes that the majority of Applicants arguments appear to be directed to the references individually not providing motivation to make the claimed invention. However, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). With regards to the motivation, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding

of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant, the Examiner recognizes that both McMahan et al. and Molecular Probes teach a heterobifunctional conjugate comprising a polydentate chelator, a linker and a detectable moiety, but do not explicitly teach that the metal ion is Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} or that the binding solution is in a pH range of 5 to 7.0. However, the knowledge of those of skill in the art, as taught by Wagner et al., Chaga et al. and Zachariou et al., was such that the metal ion and pH of the binding solution can be easily optimized depending on what one of skill in the art was looking to detect. For example, Chaga et al. teaches that immobilized metal ion affinity chromatography, referred to herein as IMAC, is a separation principle that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein the metal ions can be divided into three categories (hard, intermediate, and soft) based on their preferential activity towards nucleophiles, wherein hard metals such as Fe3+, Ca2+, Al3+ show preference for oxygen, soft metals such as Cu+, Hg2+, ect. prefer sulfur, and intermediate metals such as Cu2+, Ni2+, Zn2+, Co2+ coordinate to nitrogen, oxygen and sulfur (page 314, 2.Metal ion affinity). Similarly, Chaga et al .teach that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu2+ at neutral pH which is further confirmed by Zachariou et al. (see above). As such, the instant rejection is maintained.

Claims 1-2, 4, 6-14 and 41-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record), as evidenced by Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737, *of record*), in view of Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a polydentate chelator moiety and a detectable moiety conjugated to the polydentate chelator moiety via a PEG spacer group. With regards to the polydentate chelator moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA). With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. Etheshami discloses (page 123, Chapter 5) a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA and its application in protein purification and characterization using a two phase system. Moreover, the dissertation teaches the effect of IDA in these biochelates in a two phase system for the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin (page 126). In particular, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. Lastly, the reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20). Thus, while Etheshami does not specifically teach that the conjugate is soluble in an aqueous solution, the claimed functional limitation would be an inherent property of reference conjugate because as evidenced by Ehteshami *et al.* (supra), the presence of the PEG spacer between the chelator-metal ion moiety and the detectable label provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15).

As such, Etheshami teach a heterobifunctional conjugate comprising a polydentate chelator, a linker and a detectable moiety. However, Etheshami et al. does not explicitly teach that the metal ion is Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} or that the binding solution is in a pH range of 5 to 7.0.

Chaga et al. reviews twenty-five years of immobilized metal ion affinity chromatography (Title). In particular, Chaga et al. teaches that immobilized metal ion affinity chromatography, referred to herein as IMAC, is a separation principle that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein the metal ions can be divided into three categories (hard, intermediate, and soft) based on their preferential activity towards nucleophiles,

wherein hard metals such as Fe3+, Ca2+, Al3+ show preference for oxygen, soft metals such as Cu+, Hg2+, ect. prefer sulfur, and intermediate metals such as Cu2+, Ni2+, Zn2+, Co2+ coordinate to nitrogen, oxygen and sulfur (page 314, 2.Metal ion affinity). For example, the reference teaches that IMAC has seen extensive work in the purification of proteins from complex biological samples such as the use of Cu2+, Ni2+ and Zn2+ for the purification of proteins having exposed Histidine residues, as well as, the use of Fe3+ and Ga3+ for the enrichment of phosphorylated proteins and peptides (page 315, Historical development of IMAC, in particular, last paragraph of page 315, 1st paragraph of 316 and 3rd full paragraph of page 317). The reference further teaches that there are only a few commercially available adsorbents such as IDA and NTA which offer a maximum of tri-(IDA) or tetra (NTA) complexes with the metal ion (page 318, Versatility of the chelating ligands). Lastly, the reference teaches that different absorption selectivity's for a protein within the same sample can be achieved based on whether one uses a hard or intermediate immobilized metal ion. For example, the reference teaches that immobilized Fe3+ would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu2+ at neutral pH (page 320, Metal ion type).

Zachariou et al. teach the binding properties of immobilised O-phosphoserine (im-OPS) and 8-hydroxyquinoline (im-8-HQ) with immobilised iminodiacetic acid, also referred to as IDA, as the control system in combination with the hard Lewis metal ions, Al3+, Ca2+, Fe3+, Yb3+, and the borderline metal ion, Cu2+, over a pH range of 5.5 to 8.0 (abstract). With regards to the pH, the reference teaches that with a incubation/equilibrium buffer of 0.5 M or 0.06M ionic strength, fewer proteins bound to these hard Lewis metal ion IMAC adsorbents as the pH became increasingly alkaline, which is opposite to what is observed with protein with the borderline Lewis metal ion IMAC systems (page 111, 1st column, last paragraph bridging 2nd column).

Thus, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the reference so as to substitute the metal ion which coordinates to the heterobifunctional conjugate as taught by Etheshami et al to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by Chaga et al., that different metals such as hard Lewis metals may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

Similarly, it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to use a lower the pH of the binding solution when detecting proteins using hard Lewis metal ions such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+} because the prior art recognizes, as taught by both Chaga and Wagner, that hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+}, Ni^{2+}, Zn^{2+}, Co^{2+}.

In response to this rejection, Applicants reiterate their arguments from above that the references provide no motivation for one of skill in the art to employ the recited metal ions under the recited pH conditions.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Claims 36, 37-39 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record), as evidenced by Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737, *of record*), in view of Chaga et al. (J. Biochem. Biophys. Methods 2001; 49: 313-334, published on-line 10/2001) and Zachariou et al. (Journal of Chromatography A 2000: 890; 95-116), as applied to claims 1-2, 4, 6-14 and 41-46 above, and in further view of Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*).

Etheshami in view of Chaga et al. and Zachariou et al. teach, as described above, a heterobifunctional reagent composition comprising a conjugate comprising a polydentate chelator moiety linked to a detectable moiety via a PEG spacer group and a binding solution having a pH of 5.0 to 7.0, wherein the polydentate chelator is coordinated to a hard Lewis metal ion such as Fe^{3+}, Al^{3+}, Yb^{3+} or Ga^{3+}. The combination further teaches that the conjugates are useful for the purification of proteins such as phosphoroproteins, wherein hard Lewis metals such as Fe3+ and Ga3+ are useful for the enrichment of phosphorylated proteins and peptides

Etheshami in view of Chaga et al. and Zachariou et al. does not explicitly teach a kit comprising the components as described above.

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards

to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit.

Thus, it would have been prima facie obvious to one of skill in the art at the time the invention was made to package the chelated metal conjugate as taught by Etheshami in view of Chaga et al. and Zachariou et al. into a kit useful for the detection of a polypeptide fragments in view of the teachings of Molecular Probes because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time the invention was made would have been motivated to make a kit useful for the detection of polypeptides because standard kits enhance the probability of reproducibility and efficiency of the detection process, and further, provide for increased marketability, convenience, reliability and economy.

In response to this rejection, Applicants reiterate their arguments from above that the references provide no motivation for one of skill in the art to employ the recited metal ions under the recited pH conditions.

These arguments have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Therefore, No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642